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Aventis Pharma Deutschland GmbH DEAV2003/0017 Dr.WI

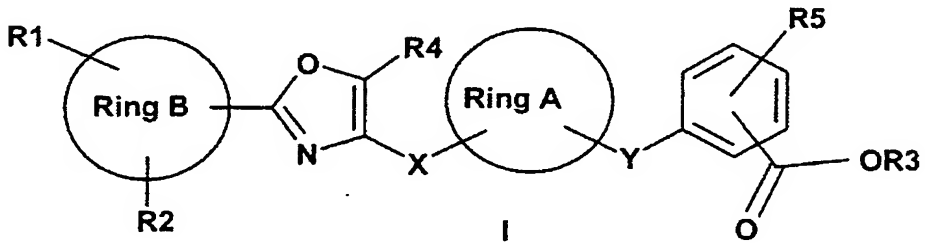
Diarylcycloalkyl derivatives, process for their preparation and their use as pharmaceuticals

The invention relates to diarylcycloalkyl derivatives and to their physiologically acceptable salts and physiologically functional derivatives.

Compounds of a similar structure have already been described in the prior art for the treatment of hyperlipidemia and diabetes (WO 2000/64876 (HOE 1999/S 004) and PCT/EP 02/09221 (DEAV2001/0053K)).

It was an object of the invention to provide compounds having a therapeutically exploitable triglyceride-lowering action and a favorable effect on lipid and carbohydrate metabolism, in particular for syndromes of dyslipidemias, type II diabetes and the metabolic syndrome/syndrome X. It was a particular object to provide compounds having improved action compared with the compounds of PCT/EP 02/09221. This was to be achieved, in particular, by activating the PPARα receptor.

Accordingly, the invention relates to compounds of the formula I



I

in which

Ring A is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl; or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3$-$C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

c) in the case ring B = a) and R4 = phenyl:
$(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

c) in the case ring B = a) and R1 = a):
$(C_1$-$C_6)$-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is $(C_1\text{-}C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

Y is $(C_1\text{-}C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

and their physiologically acceptable salts.

Preference is given to compounds of the formula I in which

Ring A is $(C_3\text{-}C_8)$-cycloalkanediyl or $(C_3\text{-}C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3\text{-}C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, $OCF_2\text{-}CHF_2$, O-phenyl, O-$(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $OCF_2\text{-}CF_3$, SCF_3, $OCF_2\text{-}CHF_2$, O-phenyl, $(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_3)$-alkyl;

c) in the case ring B = a) and R4 = phenyl:
$(C_1\text{-}C_6)$-alkyl or O-$(C_1\text{-}C_6)$-alkyl;

R is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

c) in the case ring B = a) and R1 = a):
$(C_1$-$C_6)$-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is CH_2-O;

Y is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms.

Preference is furthermore given to compounds of the formula I in which

Ring A is $(C_3$-$C_8)$-cycloalkanediyl in which one carbon atom may be replaced by an oxygen atom;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3$-$C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

b) in the case ring B = b):

H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1 = a):
(C_1-C_6)-alkyl;

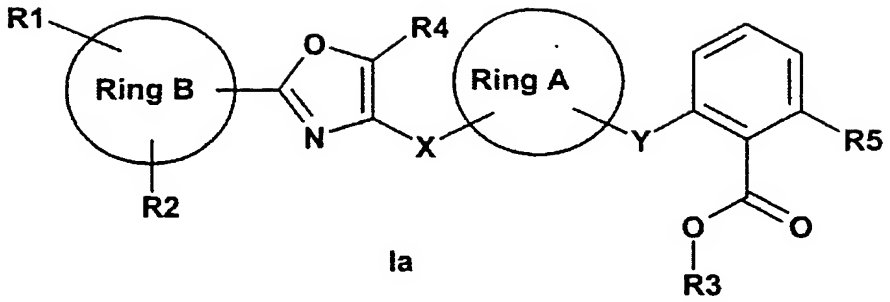
R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

R3 is H or (C_1-C_6)-alkyl;

X is CH_2-O;

Y is CH_2-O.

Particular preference is given to compounds of the formula Ia



Ia

in which ring A, ring B, R1, R2, R3, R4, R5, X and Y are as defined above.

Particular preference is furthermore given to compounds of the formula Ia in which

R3 is H and

R5 is methyl

or

to compounds of the formula Ia in which

Ring A is $(C_5\text{-}C_7)$-cycloalkanediyl;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3\text{-}C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, $OCF_2\text{-}CHF_2$, O-phenyl, O-$(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $OCF_2\text{-}CF_3$, SCF_3, $OCF_2\text{-}CHF_2$,

O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1/R2 = a):
(C_1-C_6)-alkyl;

R5 is methyl;

R3 is H;

X is CH_2-O;

Y is CH_2-O.

Very particular preference is given to compounds of the formulae I and Ia

in which the central cycloalkanediyl ring is attached 1,3-cis.

The invention embraces compounds of the formulae I and Ia in the form of their racemates, racemic mixtures and pure enantiomers, and also their diastereomers and mixtures thereof.

The alkyl radicals in the substituents R1, R2, R3, R4 and R5 can be straight-chain or branched.

A heteroaromatic ring is to be understood as meaning both mono- and bicyclic rings, in particular those which contain 1 to 4 nitrogen atoms and/or 1 oxygen or 1 sulfur atom, such as, for example: furan, thiophene, thiazole, oxazole, thiadiazole, triazole, pyridine, triazine, quinoline, isoquinoline, indole, benzothiophene, benzofuran, benzotriazole. Aromatic rings can be mono- or bicyclic and also fused, such as, for example, naphthyl, benzo[1,3]dioxole, dihydrobenzo[1,4]dioxine.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater solubility in water compared with the starting or base compounds. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acids. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester which is able, on administration to a mammal such as, for example, to a human, to form (directly or indirectly) a compound of the formula I or

an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves have activity or not.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the scope of the invention and are a further aspect of the invention.

All references hereinafter to "compound(s) of formula I" refer to compound(s) of the formula I as described above, and to the salts, solvates and physiologically functional derivatives thereof as described herein.

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active compound. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable

in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active compound. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, wafers, suckable tablets or tablets, each of which contain a defined amount of the compound of formula I; as powders or granules, as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active compound and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or

molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one or more surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound which is in powder form and is moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

The pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

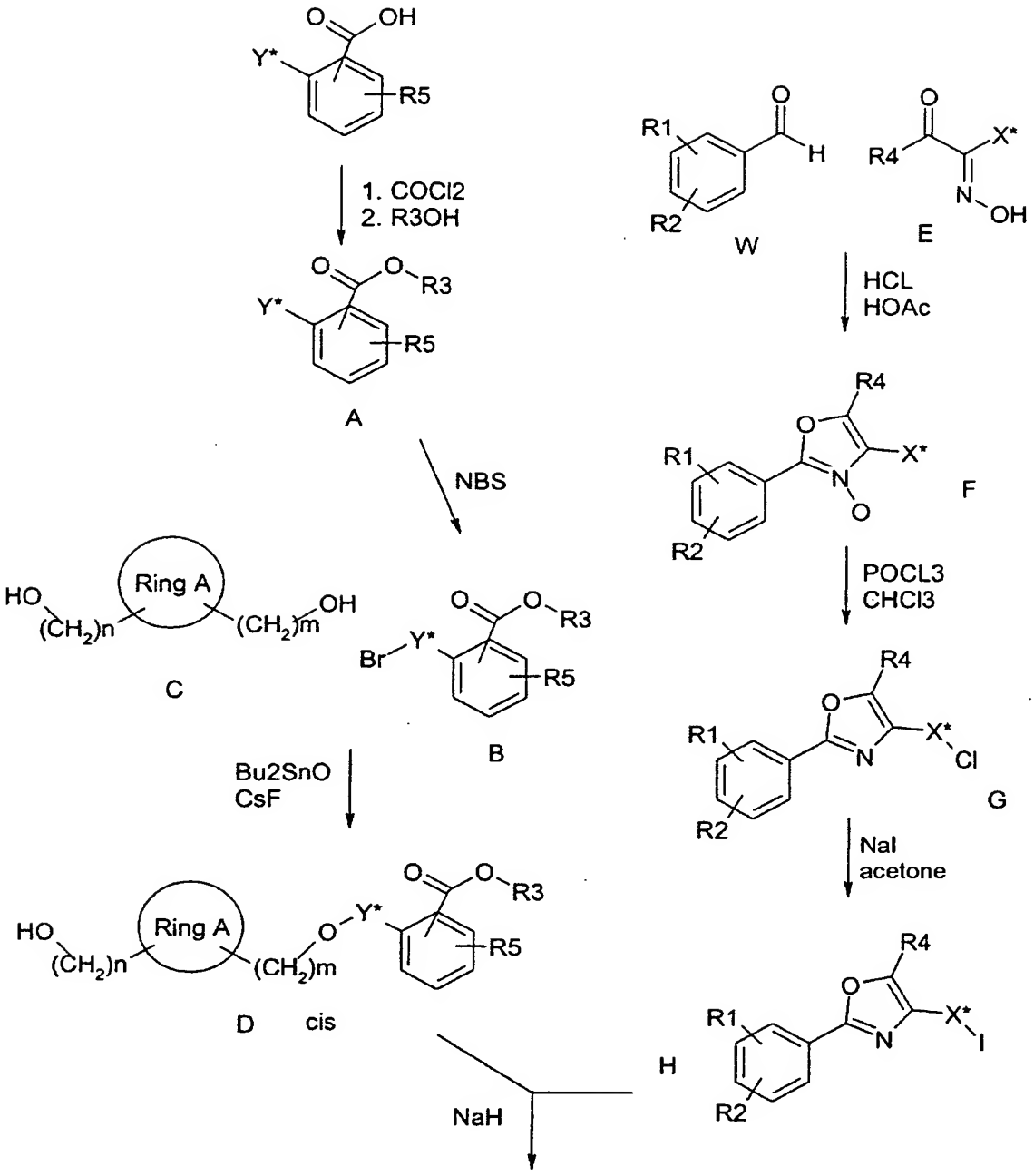
Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

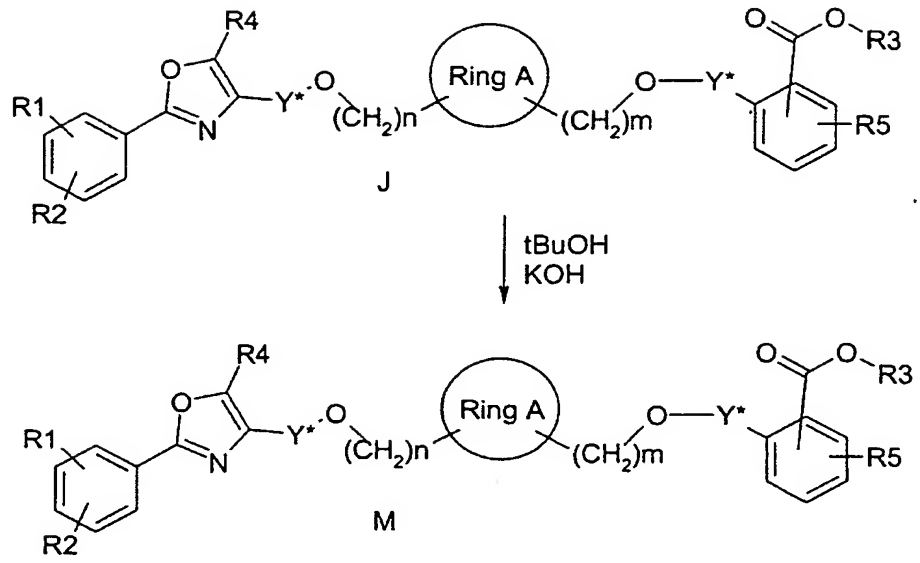
Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, crème, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active compound is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from

0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active compound in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active compound concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active compound to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The compounds of the formulae I and Ia can be obtained in accordance with the reaction scheme below:


1. COCl2
2. R3OH
A
NBS
B
C
Ring A
Bu2SnO
CsF
D
cis
NaH
H
W
E
HCL
HOAc
F
POCL3
CHCl3
G
NaI
acetone



Compounds of the formula A in which R3, R5 and Y have the meanings given above are reacted with NBS in an inert solvent (e.g. CCl4), giving a compound of the formula B.

The compound of the formula B is reacted with a compound of the formula C in which n and m are each 0-5, giving a compound of the formula D in which R1, R2, R4, m, n and Y have the meanings described above, at the same time component C is initially heated with dibutyltin oxide in toluene on a water separator for a number of hours and then, with addition of dimethylformamide, cesium fluoride and bromide B, converted into D by stirring at room temperature for a number of hours.

The compound of the formula E is reacted with an aldehyde of the formula W (for example benzaldehyde, thiophene- or furancarbaldehyde) to give a compound of the formula F in which R1, R2, R4 and X are as defined above; to this end, components E and F are initially dissolved in acetic acid and HCl is introduced until the reaction has gone to completion, giving compounds of the formula F.

The compound of the formula F in which R1, R2, R4 and X are as defined above is heated under reflux with POCl3 in chloroform for a number of hours, giving compounds of the formula G.

Compounds of the formula G in which R1, R2, R4 and X are as defined above are reacted with NaI in acetone under reflux for a number of hours, giving a compound of the formula H.

The compound of the formula D is reacted with a compound of formula H in which Y is as defined above, giving a compound of the formula J in which R1, R2, R4, R5, X and Y are as defined above. To establish an ether bond, D is deprotonated, for example, in a mixture of dimethylformamide and tetrahydrofuran using a strong base such as Na hydride, at room temperature, and then alkylated with component H.

The compound of the formula J is converted into compounds of the formula M in which R1, R2, R4, R5, X and Y are as defined above by hydrolyzing the ester function, for example by heating with potassium hydroxide and then alcohol (ethanol, tert-butanol), and releasing the carboxylic acid group of the formula I by acidification. This carboxylic acid group can be derivatized by customary methods into the group of the formula -(C=O)-OR3 in which R3 is as defined above.

Other compounds can be obtained accordingly or by known processes.

The compounds of the formulae I and Ia act favorably on metabolic disorders. They have a positive effect on lipid and sugar metabolism and, in particular, reduce the concentration of triglycerides, and they are suitable for preventing and treating type II diabetes and arteriosclerosis.

The compounds can be administered alone or in combination with one or more further pharmacologically active substances which, for example, act favorably on metabolic disorders and are selected, for example, from antidiabetics, antiadipose agents, antihypertensives and active compounds for treating and/or preventing complications caused by or associated with diabetes.
Particularly suitable further pharmacologically active substances are:

All antidiabetics mentioned in chapter 12 of the Rote Liste 2001. They may be combined with the compounds of the formula I according to the invention in particular for synergistic improvement of the effect. Administration of the active compound combination may take place either by separate administration of the active compounds to the patients or in the form of combination products in which a plurality of active compounds are present in one pharmaceutical preparation. Most of the active compounds listed below are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus® (see www.lantus.com) or HMR 1964, fast-acting insulins (see US 6,221,633), GLP-1 derivatives such as, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S, and orally active hypoglycemic active compounds.

The orally active hypoglycemic active compounds include, preferably, sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism, such as antihyperlipidemic active compounds and antilipidemic active compounds, compounds which reduce food intake, PPAR and PXR agonists and active compounds which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMG-CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor such as, for example, ezetimibe, tiqueside, pamaqueside.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570.

In one embodiment of the invention, the compounds of the formula I are administered in combination with PPAR alpha agonist such as, for example, GW 9578, GW 7647.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, GW 1536, AVE 8042, AVE 8134, AVE 0847, or as described in PCT/US 11833, PCT/US 11490, DE 10142734.4.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate such as, for example, fenofibrate, clofibrate, bezafibrate.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757.

In one embodiment of the invention, the compounds of the formula I are administered in combination with bile acid adsorption inhibitor (see, for example, US 6,245,744 or US 6,221,897) such as, for example, HMR 1741.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor such as, for example, JTT-705.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine, colesevelam.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see US 6,342,512) such as, for example, HMR1171, HMR1586.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor such as, for example, avasimibe.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant such as, for example, OPC-14117.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor such as, for example, NO-1886.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP citrate lyase inhibitor such as, for example, SB-204990.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor such as, for example, BMS-188494.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist such as, for example, CI-1027 or nicotinic acid.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor such as, for example, orlistat.

In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.:Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists (for example N-{4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}-naphthalene-1-sulfonamide hydrochloride (CGP 71683A)), MC4 agonists (for example N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexa-hydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxamide (WO 01/91752)), orexin antagonists (for example 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A)), H3 agonists (for example 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (for example [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (for example urocortin), urocortin agonists, β3 agonists (for example 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (for example {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)); serotonin reuptake inhibitors (for example dexfenfluramine), mixed serotoninergic and noradrenergic compounds (for example WO 00/71549), 5HT agonists (for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111)), bombesin agonists, galanin antagonists, growth hormone (for example human growth hormone), growth-hormone-releasing compounds (tert-butyl 6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), decoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors (for example WO 00/40569), PPAR modulators (for example WO 00/78312), RXR modulators or TR β agonists.

In one embodiment of the invention, the other active compound is leptin; see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

In one embodiment, the other active compound is dexamphetamine or amphetamine.

In one embodiment, the other active compound is fenfluramine or dexfenfluramine.

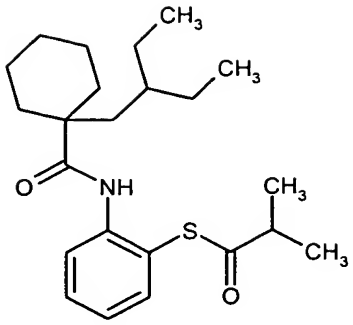
In a further embodiment, the other active compound is sibutramine.

In one embodiment, the other active compound is orlistat.

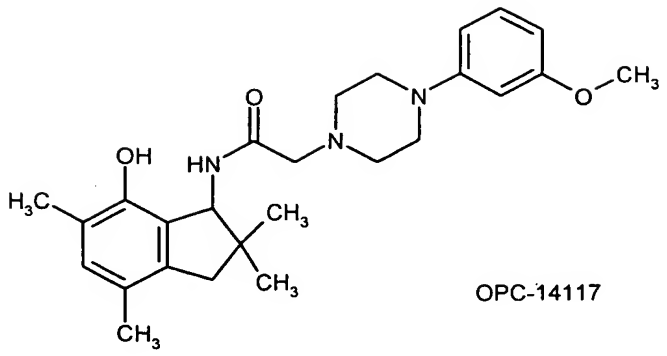
In one embodiment, the other active compound is mazindol or phentermine.

In one embodiment, the compounds of the formula I are administered in combination with dietary fiber materials, preferably insoluble dietary fiber materials (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main. Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can moreover be administered in the form of foodstuffs such as, for example, in bakery products or muesli bars.

It is self-evident that any suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.



JTT-705



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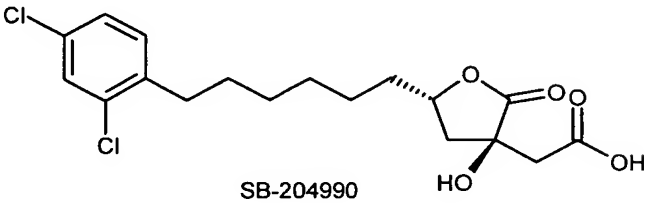

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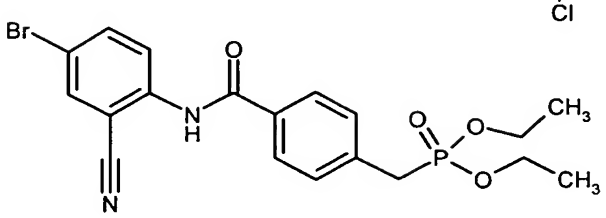

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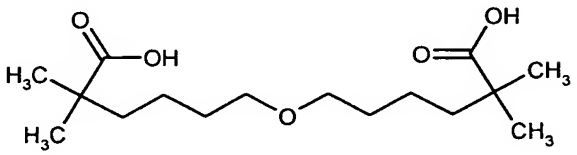

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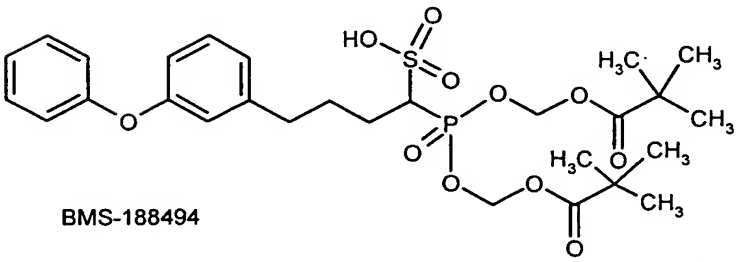

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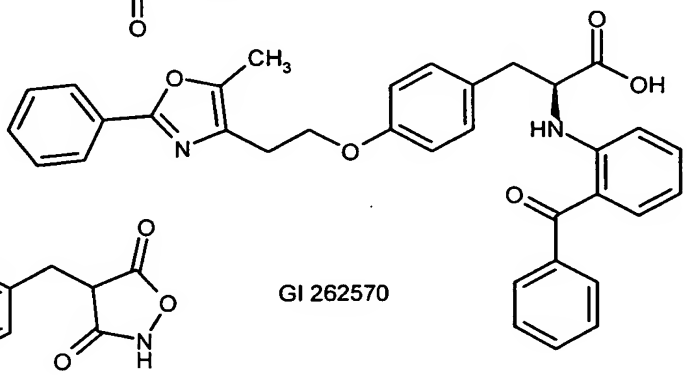

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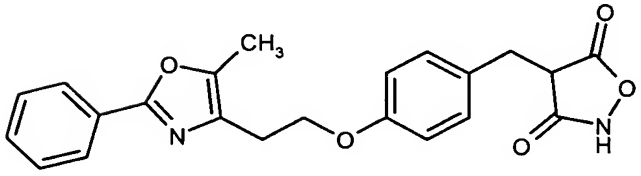


JTT-501

This invention furthermore relates to the use of compounds of the formulae I and Ia and their pharmaceutical compositions as PPAR ligand receptor binders. The PPAR ligand receptor binders according to the invention are suitable for use as agonists or antagonists of the PPAR receptor.

Peroxisome-proliferator-activated receptors (PPAR) can be divided into the three subtypes PPARα, PPARδ and PPARγ. These are encoded by different genes (Motojima, Cell Structure and Function, 18:267-277, 1993). In addition, there are two isotopes of PPARγ, PPARγ$_1$ and γ$_2$. These two proteins differ in the 30 NH_2-terminal amino acids and are the result of an alternative use of promoters and different mRNA splicing (Vidal-Puig, Jiminez, Linan, Lowell, Hamann, Hu, Spiegelman, Flier, Moller, J. Clin. Invest., 97:2553-2561, 1996).

PPAR-modulated biological processes are processes modulated by receptors or combinations of receptors which react to the PPAR receptor ligands described in this patent. These processes include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels involved in hypoglycemia/hyperinsulinism (caused, for example, by functional disorders of the pancrease beta-cells, insulin-secreting tumors and/or autoimmune hypoglycemia owing to autoantibodies against insulin, the insulin receptor or autoantibodies having a stimulating action on pancrease beta-cells), macrophage differentiation resulting in the formation of atherosclerotic plaques, in inflammable reactions, carcinogenesis, hyperplasia or adipocyte differentiation.

Adiposity is an excessive buildup of fatty tissue. Recent investigations in this field have shown that PPARγ plays a central role in gene expression and differentiation of adipocytes. Excess fatty tissue is associated with the development of serious disorders such as, for example, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, disorders of the coronary arteries, hyperlipidemia, adiposity and certain malignant syndromes. The adipocytes can, by forming tumor necrosis factor α (TNFα) and other molecules, also have an effect on glucose homeostasis.

Non-insulin-dependent diabetes mellitus (NIDDM) or type II diabetes is the more

frequent form of diabetes. About 90-95% of hyperglycemia patients suffer from this form of the disease. What is present in NIDDM is apparently a reduction of the mass of the beta cells of the pancreas, a number of different disorders of insulin secretion or reduced insulin sensitivity of the tissue. The symptoms of this form of diabetes include tiredness, frequent urination, thirst, blurred vision, frequent infections and slow healing of wounds, diabetic nerve damage and kidney diseases.

Resistance against the metabolic effects of insulin is one of the main features of non-insulin-dependent diabetes (NIDDM). Insulin resistance is characterized by reduced uptake and conversion of glucose in insulin-sensitive target organs such as, for example, adipocytes and skeletal muscles, and by reduced inhibition of hepatic gluconeogenesis. Functional insulin deficiency and the absent suppression of hepatic gluconeogenesis by insulin leads to hyperglycemia in the fasting state. The pancreas beta-cells compensate insulin resistance by increased secretion of insulin. However, the beta-cells are not able to maintain this high insulin output, so that the glucose-induced insulin secretion decreases, resulting in a deterioration of glucose homeostasis and finally in the development of manifest diabetes.

Hyperinsulinemia is likewise associated with insulin resistance, hypertriglyceridemia and increased plasma concentrations of low-density lipoproteins. Insulin resistance and hyperinsulinemia combined with these metabolic disorders is called "syndrome X" and is strongly associated with an increased risk of hypertension and disorders of the coronary arteries.

Metformin is known to the person skilled in the art as an agent for treating diabetes in humans (US patent No. 3,174,901). The primary action of metformin is reduced formation of glucose in the liver. As is known, Troglitazone® acts primarily by improving the ability of skeletal muscles to react to insulin and to take up glucose. It is known that a combination therapy of metformin and Troglitazone can be used for treating diabetes-associated disorders (DDT 3:79-88, 1998).

It has been observed that PPARγ activators, in particular Troglitazone®, convert

cancerous tissue in liposarcoma (fat tumors) into normal cells (PNAS 96:3951-3956, 1999). Furthermore, it has been proposed that PPARγ activators may be of benefit in the treatment of breast cancer and intestinal cancer (PNAS 95:8806-8811, 1998, Nature Medicine 4:1046-1052, 1998).

In addition, PPARγ activators such as, for example, Troglitazone® have also been used for treating polycystic ovarial syndrome (PCO). This syndrome, which occurs in women, is characterized by chronic anovulation and hyperandrogenism. Women with this syndrome frequently also suffer from insulin resistance and an increased risk of developing non-insulin-dependent diabetes mellitus (Dunaif, Scott, Finegood, Quintana, Whitcomb, J. Clin. Endocrinol. Metab., 81:3299, 1996).

Furthermore, it has recently been discovered that PPARγ activators increase the formation of progesterone and inhibit steroid genesis in granulosa cell cultures and may therefore be suitable for treating climacterium (US patent No. 5,814,647, Urban et al., 29 September 1998; B. Lorke et al., Journal of Endocrinology, 159, 429-39, 1998). Climacterium is defined as the syndrome of the endocrine, somatic and psychological changes which occur in women at the end of the reproductive phase.

Peroxisomes are cellular organelles involved in the control of the redox potential and oxidative stress in cells by metabolizing a large number of substrates such as, for example, hydrogen peroxide. A number of disorders are associated with oxidative stress. Thus, for example, inflammable reactions to tissue damage, pathogenesis of emphysemia, ischemia-associated organ damage (shock), doxorubicin-induced heart damage, drug-induced hepatotoxicity, atherosclerosis and lung damage caused by hyperoxia are in each case associated with the formation of reactive oxygen species and changes of the reductive capability of the cell. Accordingly, it has been proposed that PPARα activators regulate inter alia the redox potential and the oxidative stress in cells and may be useful for treating these disorders (Poynter et al., J. Biol. Chem. 273, 32833-41, 1998).

It has also been found that PPARα agonists inhibit NF_KB-mediated transcription

and thus modulate various inflammatory reactions, such as, for example, the enzyme paths of inducible nitrous oxide synthase (NOS) and cyclooxygenase-2 (COX-2) (Pineda-Torra, I. et al., 1999, Curr. Opinion in Lipidology, 10, 151-9) and can therefore be used for therapeutic interventions in a large number of different inflammatory diseases and other pathological conditions (Colville-Nash et al., Journal of Immunology, 161, 978-84, 1998; Staels et al, Nature, 393, 790-3, 1998).

Peroxisome proliferators activate PPAR which, in turn, act as transcription factors and cause differentiation, cell growth and proliferation of peroxisomes. It is also presumed that PPAR activators play a role in hyperplasia and carcinogenesis and change the enzymatic properties of animal cells such as, for example, rodent cells; however, these PPAR activators appear to have only minimal negative effects on human cells (Green, Biochem. Pharm. 43(3):393, 1992). Activation of PPAR leads to a rapid increase of gamma-glutamyl transpeptidase and -catalase.

PPARα is activated by a number of medium-chain fatty acids and long-chain fatty acids and is involved in the stimulation of β-oxidation of fatty acids in tissues such as liver, heart, skeletal muscle and brown fatty tissue (Issemann and Green, ibid.; Beck et al., Proc. R. Soc. Lond. 247:83-87, 1992; Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657, 1992).

Pharmacological PPARα activators such as, for example, fenofibrate, clofibrate, genfibrozil and bezafibrate are likewise involved in the considerable reduction of plasma triglycerides and a moderate reduction of LDL cholesterol, and they are used, in particular, for treating hypertriglyceridemia, hyperlipidemia and adiposity. It is known that PPARα is also involved in inflammatory disorders (Schoonjans, K., Current Opinion in Lipidology, 8, 159-66, 1997).

The human nuclear receptor PPARδ has been cloned from a cDNA library of human osteosarcoma cells and is described completely in A. Schmidt et al., Molecular Endocrinology, 6:1634-1641 (1992). The contents of this article are hereby incorporated by reference into the present patent application. It may be pointed out that in the literature PPARδ is also referred to as PPARβ and as

NUC1, but all of these names refer to the same receptor. Thus, in A. Schmidt et al., Molecular Endocrinology, 6:1634-1641, 1992, for example, the receptor is referred to as NUC1. PPARδ is found both in embryonal and in adult tissue. It has been reported that this receptor is involved in the regulation of the expression of some fat-specific genes and therefore plays a role in the process of adipogenesis (Amri, E. et al., J. Biol. Chem. 270, 2367-71, 1995).

It is known that atherosclerotic disorders are caused by a number of factors such as, for example, hypertension, diabetes, low concentrations of high-density lipoproteins (HDL) and high concentrations of low-density lipoproteins (LDL). In addition to reducing the risks by acting on the concentration of the plasma lipids and other risk factors, PPARα agonists have direct atheroprotective actions (Frick, M.H. et al., 1997, Circulation 96:2137-2143, de Faire et al., 1997, Cardiovasc. Drugs Ther. 11 Suppl. 1:257-63).

It has recently been found that PPARδ agonists are useful for increasing HDL level and are therefore suitable for treating atherosclerotic disorders (Leibowitz et al., WO/9728149). Atherosclerotic disorders include vascular disorders, coronary heart disease, cerebrovascular disorders and disorders of the peripheral vessels. Coronary heart disease includes death by coronary heart disease, myocardial infarction and coronary revascularization. Cerebrovascular diseases include ischemic and hemorrhagic infarcts and transient ischemic attacks.

PPARγ subtypes are involved in the activation of adipocyte differentiation and do not play any role in the stimulation of peroxysome proliferation in the liver. Activation of PPARγ contributes to adipocyte differentiation by activating the adipocyte-specific gene expression (Lehmann, Moore, Smith-Oliver, Wilkison, Willson, Kliewer, J. Biol. Chem., 270:12953-12956, 1995). The DNA sequences of the PPARγ subtypes are described in Elbrecht et al., BBRC 224; 431-437 (1996). Although peroxysome proliferators including fibrates and fatty acids activate the transciptory activity of PPARs, only prostaglandin J_2 derivatives such as the arachidonic metabolite 15-deoxy-delta^{12}, 14-prostaglandin J_2 (15d-PGJ_2) have been identified as natural ligands specific for the PPARγ subtype which also binds

to thiazolidinediones. This prostaglandin activates PPARγ-dependent adipogenesis, but activates PPARα only at high concentrations (Formann, Tontonoz, Chen, Brun, Spiegelman, Evans, Cell, 83:803-812, 1995; Kliewer, Lenhard, Wilson, Patel, Morris, Lehmann, Cell, 83:813-819, 1995). This is a further indication that the subtypes of the PPAR family differ in their pharmacological reaction to ligands.

From this, it can be concluded that compounds which activate PPARα or both PPARα and PPARγ have to be effective hypotriglyceridemic drugs which can be used for treating atherosclerosis-associated dislipidemia, non-insulin-dependent diabetes mellitus, syndrome X (Staels, B. et al., Curr. Pharm. Des., 3 (1), 1-4 (1997)) and familial combined hyperlipidemia (FCH). Syndrome X is the syndrome which is characterized by a first insulin-resistant stage which causes hyperinsulinemia, dyslipidemia and reduced glucose tolerance and which can progress to non-insulin-dependent diabetes mellitus (type II diabetes) characterized by hyperglycemia. FCH is characterized by hypercholesterolemia and hypertriglyceridemia in the same patient and in the same family.

The present invention relates to compounds of the formula I suitable for modulating PPAR receptors, and for a number of other related pharmaceutical applications.

The compounds of the formulae I and Ia are suitable in particular for treating dyslipidemia, insulin resistance, type I and type II diabetes, disturbed glucose tolerance, syndrome X, obesity, eating disorders, thromboses, inflammations, cardiomyopathy and for protecting beta-cells and protection against fatty acid oxidation (see, for example, Jean-Charles Fruchart, Bart Staels and Patrick Duriez: PPARS, Metabolic Disease and Atherosclerosis, Pharmacological Research, Vol. 44, No. 5, 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

The activity of the compounds was tested as follows:

To analyze the effectiveness of substances which bind to human PPARalpha, activating it in agonistic manner, a stable transfected HEK cell line (HEK = human embryo kidney) designated here as "PPARalpha reporter cell line" is used.
The activity of PPARalpha agonists is determined in a three-day test, described below:

The PPARalpha reporter cell line is cultivated up to 80% confluence in DMEM medium (# 41965-039, Life Technologies) with the following additives: 10% cs-FCS (fetal calf serum, #SH-30068.03, Hyclone), antibiotics (0.5 mg/ml of zeozin [#R250-01, Invitrogen], 0.5 mg/ml of G418 [#10131-019, Life Technologies], 1% penicillin streptomycin solution [#15140-031, Life Technologies]) and 2 mM of L-glutamine (#25030-032, Life Technologies). Cultivation is carried out in standard cell culture bottles (# 33111, Becton Dickinson) in a cell culture incubator at 37°C and 5% CO_2. The 80% confluent cells are washed once with 30 ml of PBS (#14190-094, Life Technologies), treated with 2 ml of trypsin solution (#25300-054, Life Technologies) at 37°C for 2 min, taken up in 5 ml of the medium described above and counted in a cell counter. After dilution to 500 000 cells/ml, in each case 100 000 cells are sown into each well of a 96-well microtiter plate having a clear plastic bottom (#3610, Corning Costar). The plates are incubated in a cell incubator at 37°C and 5% CO_2 for 24 h.

The PPARalpha agonists to be tested are dissolved in DMSO at a concentration of 10 mM. This stock solution is diluted in Phenol-Red-free DMEM medium (#21063-029, Life Technologies) to which 5% of cs-FCS (#SH-30068.03, Hyclone), 2 mM of L-glutamine (#25030-032, Life Technologies) and the antibiotics already described under "seeding of the cells" (zeozin, G418, penicillin and streptomycin) had been added.

Test substances are usually tested at 11 different concentrations (10 µM; 3.3 µM; 1 µM; 0.33 µM; 0,1 µM; 0.033 µM; 0.01 µM; 0.0033 µM; 0.001 µM; 0.00033 µM and 0.0001 µM). More potent compounds are tested in concentration ranges of from 1 µM to 10 pM or 100 nM to 1 pM. From each well, the medium of the PPARalpha reporter cell line sown on day 1 is completely removed by aspiration, and immediately, the test substances diluted in medium are added to the cells. Dilution and addition of the substances can be carried out using a robot (Beckman Biomek 2000). The end volume of the test substances diluted in medium is 100 µl per well of a 96-well plate. The DMSO concentration in the assay is always below 0.1% v/v to prevent cytotoxic effects of the solvent.

To demonstrate that the assay is working in each individual plate, a standard PPARalpha agonist, which is also diluted to 11 different concentrations, is added to each plate. The test plates are incubated in an incubator at 37°C and 5% CO_2 for 24 h.

The PPARalpha receptor cells treated with the test substances are removed from the incubator and frozen at -20°C for 1 h to improve cell lysis. After the plates have thawed (thawing at room temperature for at least 30 min), 50 µl of buffer 1 (Luc-Screen kit #LS1000, PE Biosystems Tropix) are pipetted into each well and the plates are then transferred into an apparatus for measuring luminescence, fitted with a pipetting unit (Luminoscan Ascent, LabSystems). The luciferase reaction in the measurement apparatus is started by pipetting 50 µl of buffer 2 (Luc-Screen kit #LS1000, PE Biosystems Tropix) into each well of the 96-well plate. Addition of buffer to the individual wells is carried out in defined and identical time intervals following the instructions of the manufacturer (LabSystems). All samples are measured exactly 16 min after addition of buffer 2. Measurement time is 10 sec per sample.

The crude data of the apparatus for measuring luminescence are exported into a Microsoft Excel file. Dose-activity curves and EC_{50} values are calculated using the program XL.Fit according to the instructions of the manufacturer (IDBS).

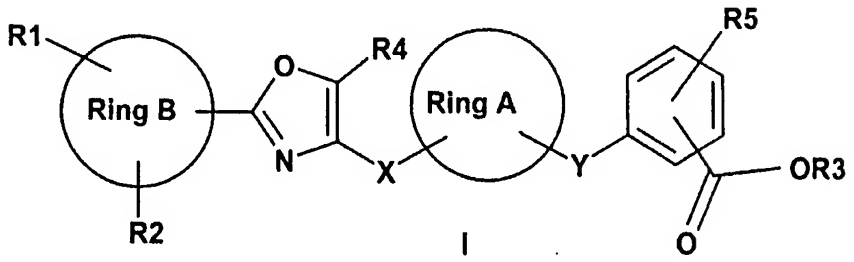
The results for the activity of the compounds of the formula I according to the invention are listed in table I below:

Table I

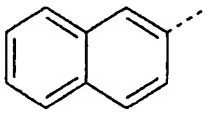
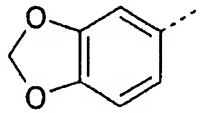
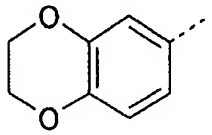
Example No.	EC50 PPARalpha [nM]
I	0.2
III	0.2
IV	0.6
X	0.3
XI	34
XII	26
XIII	0.06

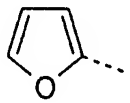
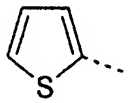
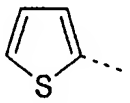
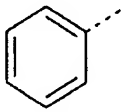
It is evident from table I that the compounds of the formula I according to the invention activate the PPARα receptor, thus effecting, analogously to clinically used fibrates, a lowering of the triglyceride concentration in the organism (see, for example, J.-Ch. Fruchard et al.: PPARS, Metabolic Disease and Atherosclerosis, Pharmacological Research, Vol. 44, No. 5, 2001; S. Kersten et al.: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; I. Pineda et al.: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

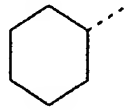
The examples given below serve to illustrate the invention, but without limiting it.



I

	R1	R2	Ring B	R4	X	Ring A	Y	R3	R5
I	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
II	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
III	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me

	R1	R2	Ring B	R4	X	Ring A	Y	R3	R5
IV	5-Me	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
V	5-Me	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
VI	4-SCF3	H	Ph	Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
VII	3-OCF2-CF2H	H	Ph	Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
VIII	4-OPh	H	Ph	Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
IX	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
X	3-O-C2H4-O-Me	5-CF3		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me

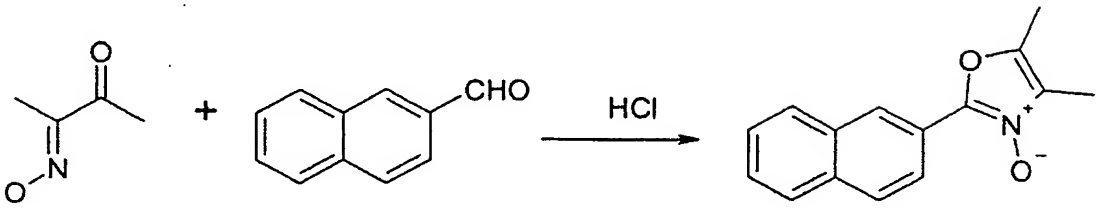
	R1	R2	Ring B	R4	X	Ring A	Y	R3	R5
XI	4-Me	H	Ph	Ph	CH2O	cis 1,3 Cy	CH2O	H	6-Me
XII	3-OMe	H	Ph	Ph	CH2O	cis 1,3 Cy	CH2O	H	6-Me
XIII	H	H		H	CH2O	cis 1,3 Cy	CH2O	H	6-Me

cis 1,3 cy means: cis-substituted cyclohexane-1,3-diyl

----: indicates the point of attachment

Example I

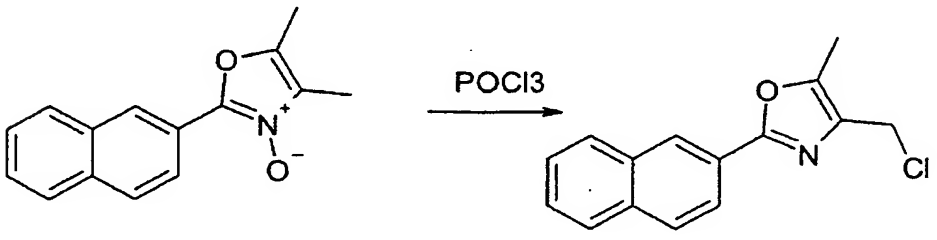
4,5-Dimethyl-2-naphthalen-2-yloxazole 3-oxide



18.4 g of diacetyl monoxime and 31.2 g of 2-naphthaldehyde are added to 50 ml of glacial acetic acid, and HCl gas is introduced with ice-cooling for 30 minutes. The product is precipitated as the hydrochloride by addition of methyl tert-butyl ether and filtered off with suction, and the precipitate is washed with methyl tert-butyl ether. The precipitate is suspended in a mixture of dichloromethane and water, and a basic pH is established using ammonia. The mixture is extracted three times with in each case 500 ml of dichloromethane and ethyl acetate, the combined organic phases are dried over MgSO4 and the solvent is then removed under reduced pressure. This gives 40.3 g of 4,5-dimethyl-2-naphthalen-2-yloxazole 3-oxide as a yellow solid.

CF15H13NO2 (239.28), MS(ESI) = 240 ($M+H^+$).

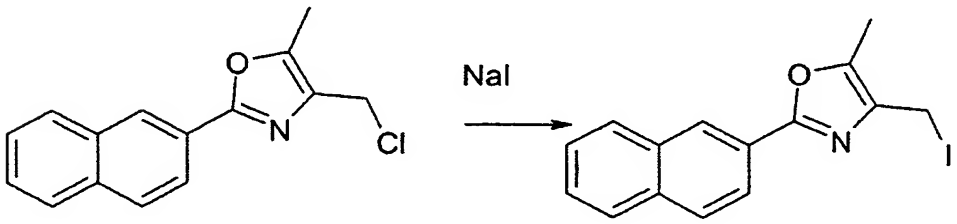
4-Chloromethyl-5-methyl-2-naphthalen-2-yloxazole



40 g of 4,5-dimethyl-2-naphthalen-2-yloxazole 3-oxide are dissolved in 200 ml of chloroform, 16.7 ml of phosphorus oxychloride are added and the mixture is

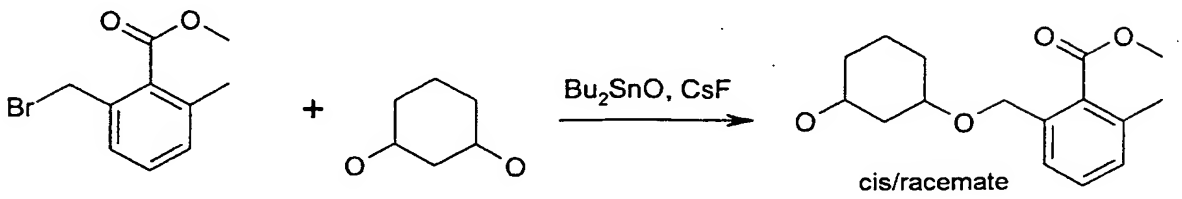
heated under reflux for 30 minutes. The reaction mixture is cooled to 0°C, a slightly alkaline pH is established using ammonia and the mixture is extracted three times with in each case 500 ml of ethyl acetate. The combined organic phases are washed with water and dried over MgSO4 and the solvent is then removed under reduced pressure. The residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 80:1 => 5:1. This gives 10.6 g of 4-chloromethyl-5-methyl-2-naphthalen-2-yloxazole as a colorless solid. C15H12ClNO (257.72), MS(ESI): 258 ($M+H^+$).

4-Iodomethyl-5-methyl-2-naphthalen-2-yloxazole



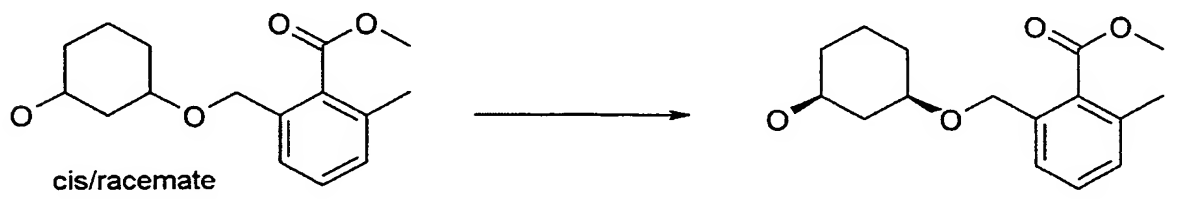
1.8 g of 4-chloromethyl-5-methyl-2-naphthalen-2-yloxazole and 3 g of sodium iodide in 150 ml of acetone are heated under reflux for 2 hours. After the reaction mixture has been cooled, 300 ml of methyl tert-butyl ether are added, the mixture is washed three times with saturated Na2S2O3 solution and dried over MgSO4 and the solvents are then removed under reduced pressure. This gives 2.7 g of 4-iodomethyl-5-methyl-2-naphthalen-2-yloxazole as a light-yellow solid. C15H12INO (349.17), MS(ESI): 350 ($M+H^+$).

Methyl 2-(cis-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate



8.7 g of 1,3-cyclohexanediol and 12 g of dibutyltin oxide are dissolved in 600 ml of toluene and, in a water separator, heated under reflux. During the reaction, the reaction volume is reduced to half the original volume. After 4 hours, the reaction mixture is cooled to room temperature, and 300 ml of DMF, 9.0 g of methyl 2-bromomethyl-6-methylbenzoate and 9.4 g of cesium fluoride are added. The mixture is stirred at room temperature for 12 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated NaCl solution. The organic phase is dried over magnesium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel ((n-heptane/ethyl acetate = 50:1 -> 1:2). This gives 6 g of methyl 2-(cis-3-hydroxy-cyclohexyloxymethyl)-6-methylbenzoate as an oil. $C_{16}H_{22}O_4$ (278.35), MS(ESI): 279 ($M + H^+$).

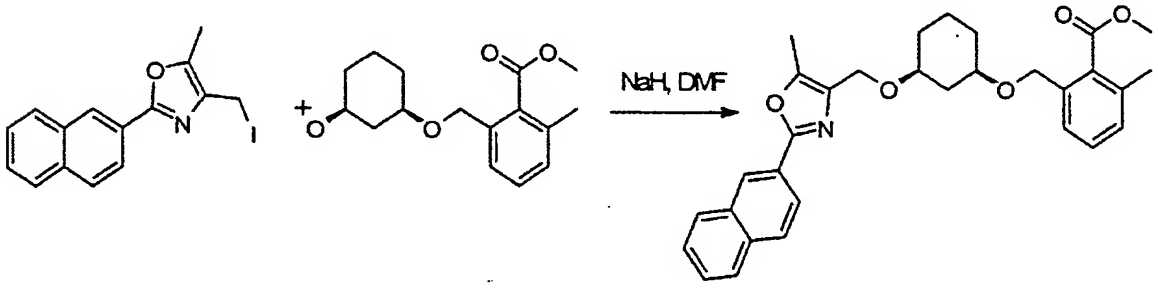
Methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate



8 g of methyl 2-(cis-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate are dissolved in 100 ml of vinyl acetate, and 1 g of Candida antartika lipase B is added. The mixture is stirred at room temperature for seven hours and the enzyme

is then filtered off and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel ((n-heptane/ethyl acetate = 10:1). This gives 3.9 g of the alcohol methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate as a colorless oil. $C_{16}H_{22}O_4$ (278.35), MS(ESI): 279 ($M + H^+$) ee = 98% ((Chiralpak AD/2 250x4.6; n-heptane:ethanol:methanol = 25:1:0.5 + 0.1% trifluoroacetic acid, R_t = 8.9 min; retention time of the enantiomer: R_t = 9.9 min.).

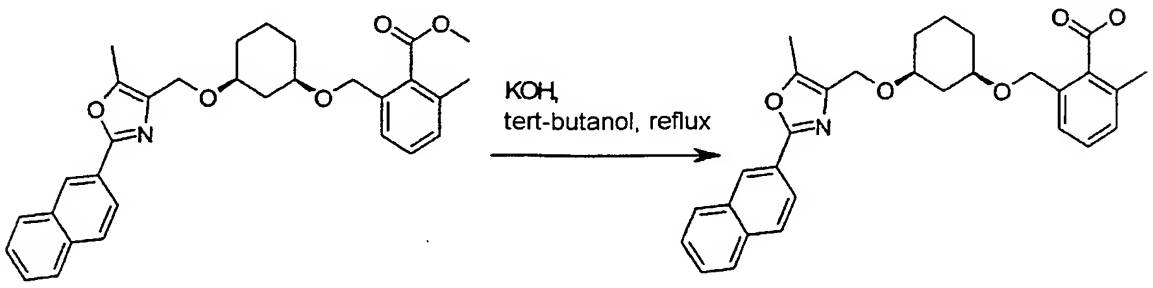
Methyl 2-methyl-6-[(1R,3S)-3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)-cyclohexyloxymethyl]benzoate



At room temperature, 50 mg of a 60% strength suspension of sodium hydride are added to a solution of 200 mg of methyl 2-((1R,3S)-3-hydroxycyclohexyloxy-methyl)-6-methylbenzoate in 5 ml of dimethylformamide, and 380 mg of 4-iodo-methyl-5-methyl-2-naphthalen-2-yloxaxole are then added. After one hour, methyl tert-butyl ether is added and the mixture is extracted with water. The organic phase is dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives 94 mg of methyl 2-methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclo-hexyloxymethyl]benzoate as a light-yellow oil.

C31H33NO5 (499.61), MS(ESI): 500 ($M + H^+$).

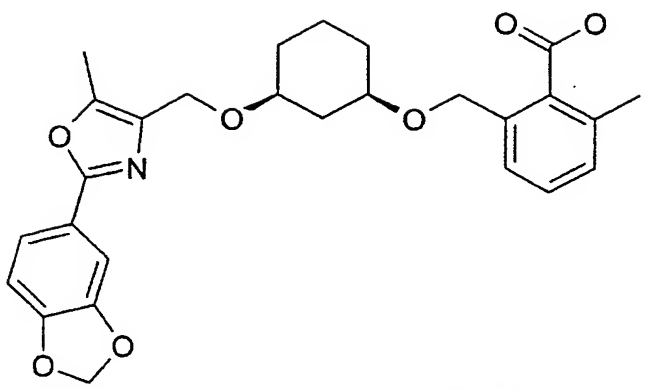
2-Methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid



94 mg of methyl 2-methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy]cyclohexyloxymethyl]benzoate are stirred at 90°C in a mixture of 10 ml of tert-butanol and 1 ml of 10 N potassium hydroxide solution. After two days, the mixture is acidified with hydrochloric acid and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives 72 mg of 2-methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid as an amorphous solid. $C_{30}H_{31}NO_5$ (485.59), MS(ESI): 486 ($M + H^+$).

Example II

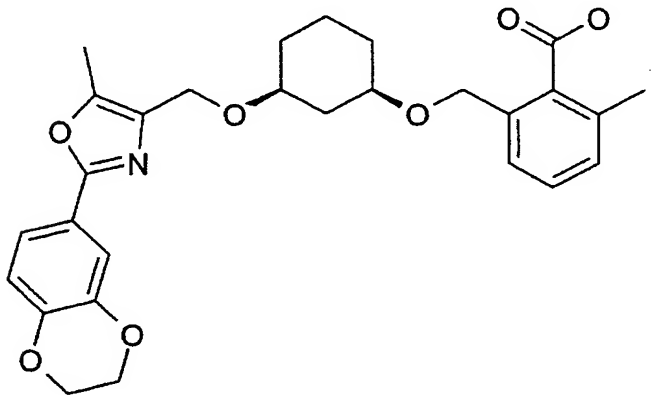
Analogously to **Example I**, diacetyl monoxime, benzo[1,3]dioxole-5-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-[(1R,3S)-3-(2-benzo[1,3]dioxol-5-yl-5-methyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-6-methylbenzoic acid.



$C_{27}H_{29}NO_7$(479.53), MS(ESI): 480 ($M + H^+$).

Example III

Analogously to **Example I**, diacetalymonoxime, 2,3-dihydrobenzo[1,4]dioxine-6-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave 2-[(1R,3S)-3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-6-methylbenzoic acid.

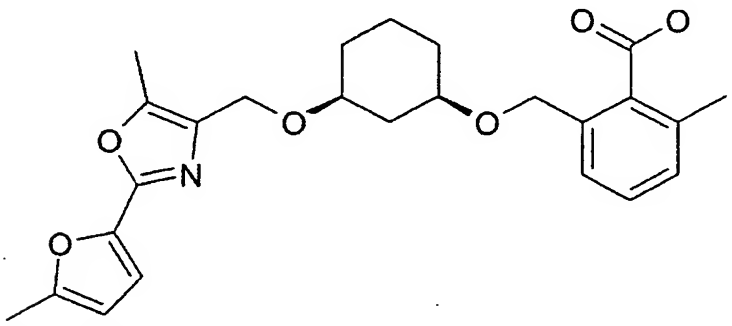


$C_{28}H_{31}NO_7$(493.56), MS(ESI): 494 ($M + H^+$).

Example IV

Analogously to **Example I**, diacetyl monoxime, furan-2-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-methyl-6-

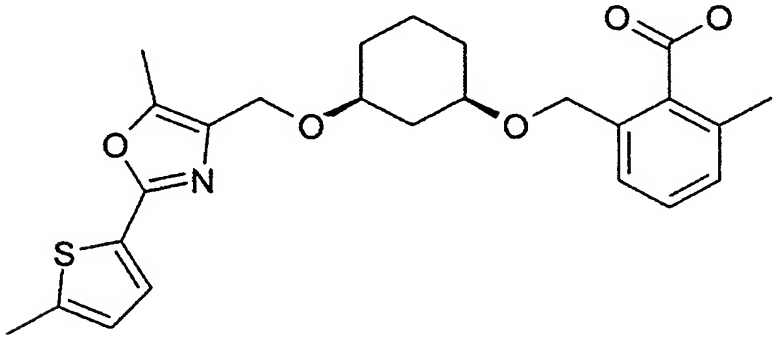
{(1R,3S)-3-[5-methyl-2-(5-methylfuran-2-yl)oxazol-4-ylmethoxy]cyclohexyloxy-methyl}benzoic acid.



$C_{25}H_{29}NO_6$(439.51), MS(ESI): 440 ($M + H^+$).

Example V

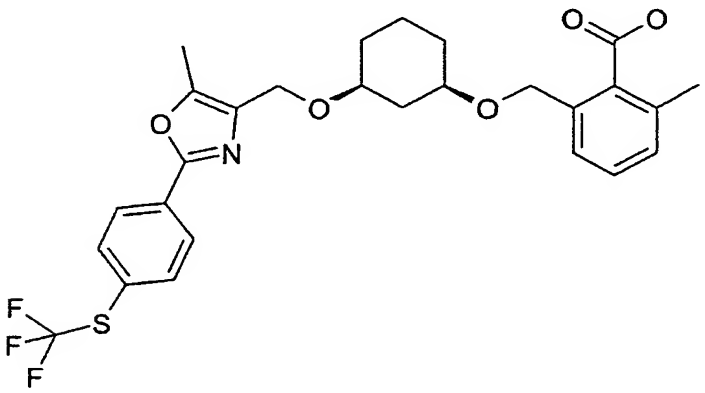
Analogously to **Example I**, diacetyl monoxime, 5-methylthiophene-2-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-methyl-6-{(1R,3S)-3-[5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-ylmethoxy]-cyclohexyloxymethyl}benzoic acid.



$C_{25}H_{29}NO_5S$(455.58), MS(ESI): 456 ($M + H^+$).

Example VI

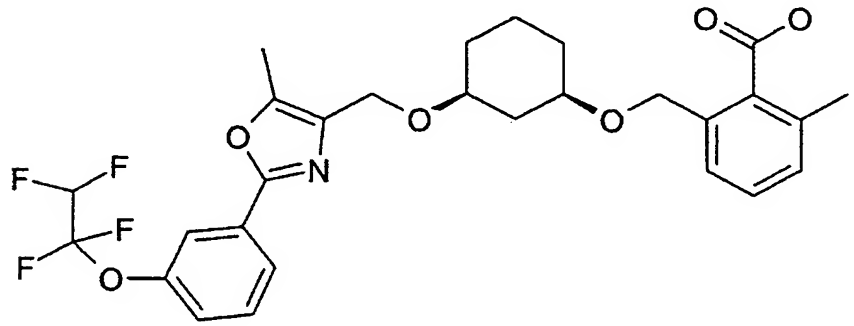
Analogously to **Example I**, diacetyl monoxime, 4-trifluoromethylsulfanyl-benzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave 2-{(1R,3S)-methyl-6-{3-[5-methyl-2-(4-trifluoromethylsulfanyl-phenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}benzoic acid.



$C_{27}H_{28}F_3NO_5S$(535.58), MS(ESI): 536 ($M + H^+$).

Example VII

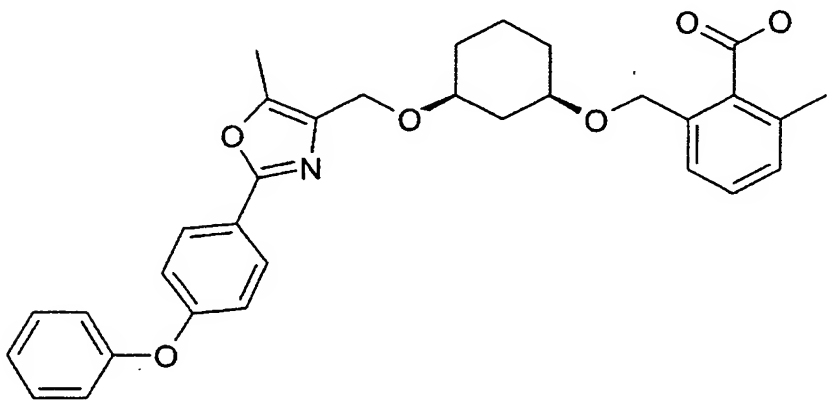
Analogously to **Example I**, diacetyl monoxime, 3-pentafluoroethyloxy-benzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave 2-{(1R,3S)-methyl-6-(3-{5-methyl-2-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]oxazol-4-ylmethoxy}cyclohexyloxymethyl)benzoic acid.



$C_{28}H_{29}F_4NO_6$(551.54), MS(ESI): 552 ($M + H^+$).

Example VIII

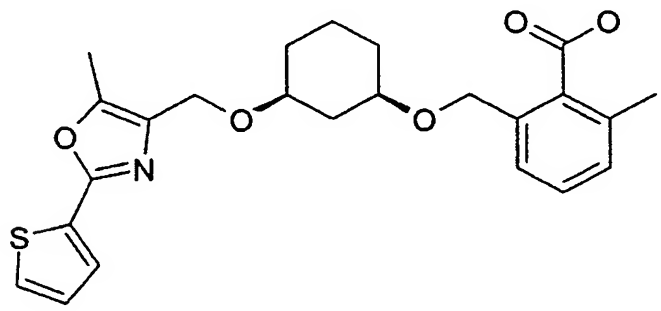
Analogously to **Example I**, diacetyl monoxime, 4-phenoxybenzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-{(1R,3S)-methyl-6-{3-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}benzoic acid.



$C_{32}H_{33}NO_6$(527.62), MS(ESI): 528 ($M + H^+$).

Example IX

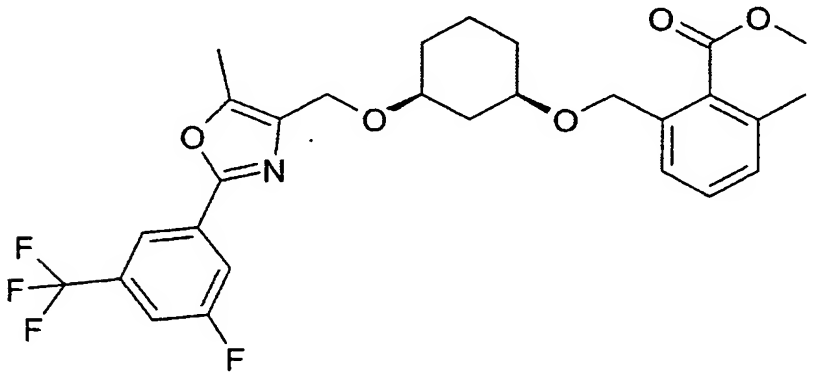
Analogously to **Example I**, diacetyl monoxime, thiophene-2-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-{(1R,3S)-methyl-6-[3-(5-methyl-2-thiophen-2-yloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid.



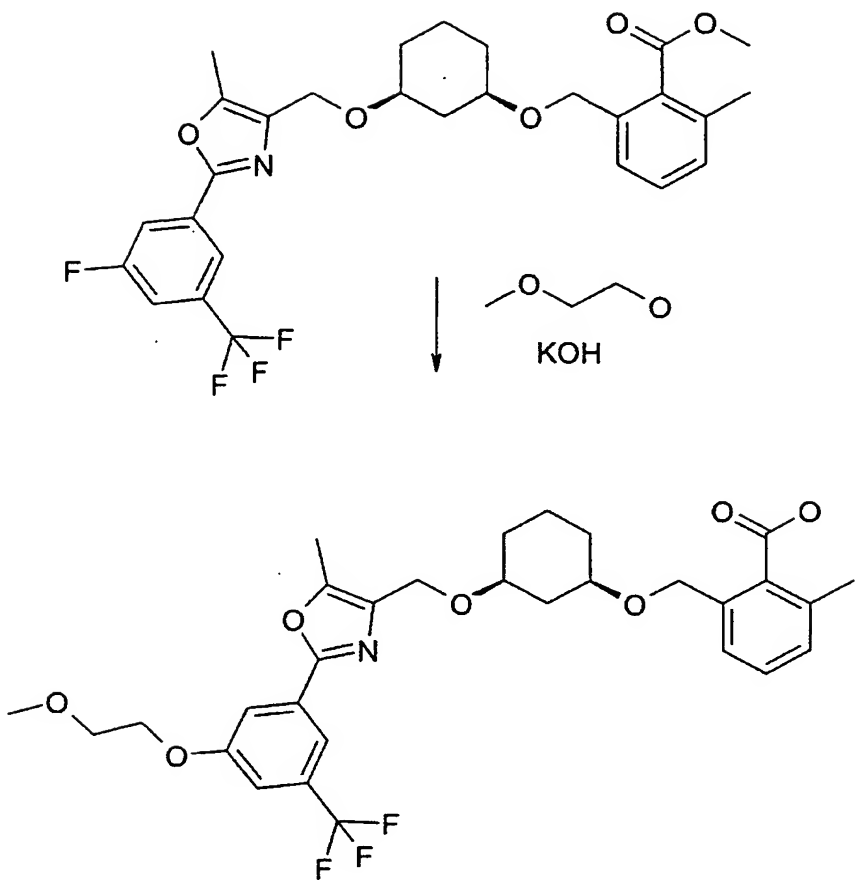
$C_{24}H_{27}NO_5S$(441.55), MS(ESI): 442 ($M + H^+$).

Example X

Analogously to **Example I**, diacetyl monoxime, 3-fluoro-5-trifluoromethyl-benzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave methyl 2-{(1R,3S)-{3-[2-(3-fluoro-5-trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoate.



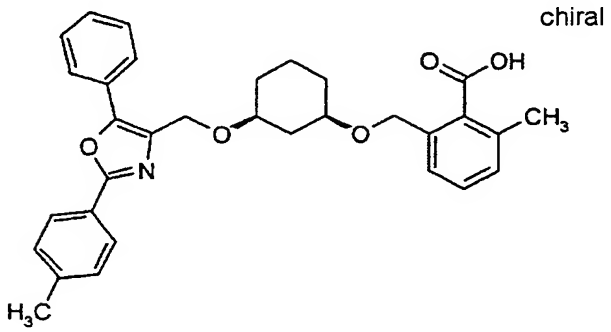
C28H29F4NO5 (535.54), MS(ESI): 536 ($M + H^+$).



A mixture of 128 mg of methyl 2{(1R,3S)-{3-[2-(3-fluoro-5-trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoate, 5 ml of ethylene glycol monomethyl ether and 0.6 ml of 10N KOH were heated under reflux for 24. After cooling, the mixture is acidified with hydrochloric acid and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulphate, the solvent is removed under reduced pressure and the residue is purified by RP-HPLC. This gives 56 mg of 2-{(1R,3S)-(3-{2-[3-(2-methoxyethoxy)-5-trifluoromethylphenyl]-5-methyloxazol-4-ylmethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid as a colorless oil of molecular weight $C_{29}H_{32}F_3NO_7$ (563.58), MS(ESI): 564 ($M + H^+$).

Example XI

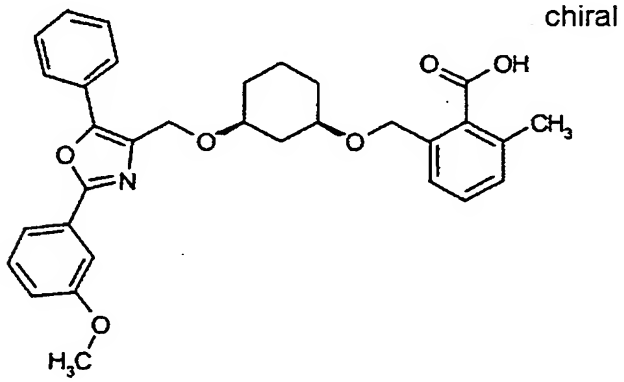
Analogously to **Example I**, 1-phenyl-1,2-propanedione 2-oxime, p-tolualdehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-methyl-6-[(1R,3S)-3-(5-phenyl-2-p-tolyloxazol-4-ylmethoxy)-cyclohexyloxymethyl]benzoic acid.



C32H33NO5 (511.62), MS(ESI) = 512 ($M+H^+$).

Example XII

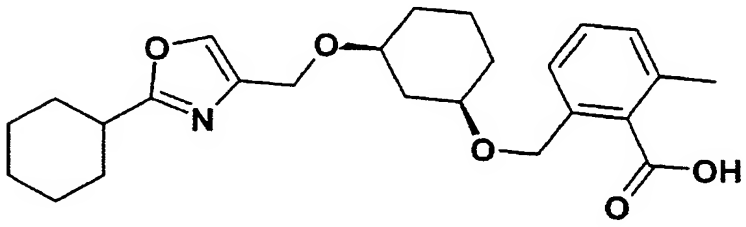
Analogously to **Example I**, 1-phenyl-1,2-propanedione 2-oxime, m-anisaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-{(1R,3S)-3-[2-(3-methoxyphenyl)-5-phenyloxazol-4-ylmethoxy]cyclohexyloxy-methyl}-6-methylbenzoic acid.



C32H33NO6 (527.62), MS(ESI) = 528 ($M+H^+$).

Example XIII

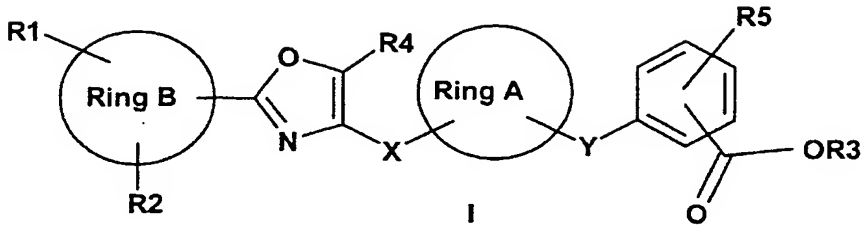
Analogously to **Example I**, 2-cyclohexyl-4-iodomethyloxazole and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-[(1R,3S)-3-(2-cyclohexyloxazol-4-ylmethoxy)cyclohexyloxymethyl)-6-methylbenzoic acid.



$C_{25}H_{27}NO_5$(421.50); MS(ESI): 422 ($M+H^+$).

We claim: DEAV2003/0017 Dr. WI

1. A compound of the formula I



I

in which

Ring A is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl; or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3$-$C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

c) in the case ring B = a) and R4 = phenyl:
$(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

c) in the case ring B = a) and R1 = a):
$(C_1$-$C_6)$-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

Y is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

and its physiologically acceptable salts.

2. A compound of the formula I as claimed in claim 1, wherein

Ring A is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O

and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1 = a):
(C_1-C_6)-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

R3 is H or (C_1-C_6)-alkyl;

X is CH_2-O;

Y is (C_1-C_6)-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms.

3. A compound of the formula I as claimed in claim 1 or 2, wherein

Ring A is (C_3-C_8)-cycloalkanediyl in which one carbon atom may be replaced by an oxygen atom;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1 = a):
(C_1-C_6)-alkyl;

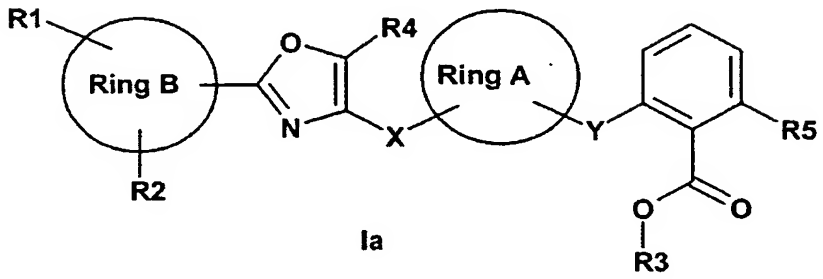
R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is CH_2-O;

Y is CH_2-O.

4. A compound of the formula Ia



Ia

in which ring A, ring B, R1, R2, R3, R4, R5, X and Y are as defined in claims 1 to 3.

5. A compound of the formula 1a as claimed in claim 4 in which

R3 is H and

R5 is methyl.

6. A compound of the formula Ia as claimed in claim 4 or 5, in which

Ring A is $(C_5$-$C_7)$-cycloalkanediyl;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain

one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1/R2 = a):
(C_1-C_6)-alkyl;

R5 is methyl;

R3 is H;

X is CH_2-O;

Y is CH_2-O.

7. A compound of the formula I or Ia as claimed in any of claims 1 to 6, wherein the central cycloalkanediyl ring is attached 1,3-cis.

8. A pharmaceutical, comprising one or more compounds as claimed in one or more of claims 1 to 7.

9. A pharmaceutical comprising one or more compounds as claimed in one or more of claims 1 to 7 and one or more active compounds.

10. A pharmaceutical, comprising one or more compounds as claimed in one or more of claims 1 to 7 and one or more lipid- or triglyceride-lowering active compounds.

11. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of disorders of the lipid metabolism.

12. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of type II diabetes.

13. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of syndrome X.

14. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of disturbed glucose tolerance.

15. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of eating disorders.

16. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of obesity.

17. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of cardiomyopathy.

18. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of cardiac insufficiency.

19. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of osteoporosis.

20. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of atherosclerosis.

21. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of Alzheimer's disease.

22. The use of the compounds as claimed in one or more of claims 1 to 7 for preparing a medicament for the treatment of inflammations.

23. The use of compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for preparing a medicament for the treatment of disorders of the lipid metabolism.

24. The use of compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for preparing a medicament for the treatment of type II diabetes.

25. The use of compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for preparing a medicament for the treatment of syndrome X.

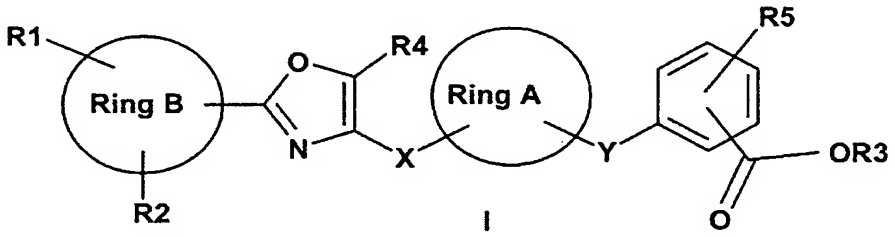
26. A process for preparing a pharmaceutical comprising one or more compounds as claimed in one or more of claims 1 to 7, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.

Abstract DEAV2003/0017 Dr.WI

Diarylcycloalkyl derivatives, process for their preparation and their use as pharmaceuticals

The invention relates to diarylcycloalkyl derivatives and to their physiologically acceptable salts, racemates and physiologically functional derivatives.

What is described are compounds of the formula I,



I

in which the radicals are as defined, and their physiologically acceptable salts and processes for their preparation. The compounds have lipid- and/or triglyceride-lowering properties and are suitable, for example, for the treatment of disorders of the lipid metabolism, of type II diabetes and of syndrome X.